

NIEHS News

Low-Level Estrogenic Effects

At the NIEHS-sponsored "Estrogens in the Environment II" conference held in Washington, DC, last winter, the issue of estrogenic chemicals in the environment and their possible adverse effects on reproduction was addressed. Estrogens are hormones that induce estrus and are responsible for the development and maintenance of female secondary sex characteristics. Chemical substances that exhibit biological activities similar to estrogens are considered estrogenic chemicals.

At the conference, researchers presented evidence of decreased reproductive capacity, feminization of male behavior, and feminization of male reproductive tissues in birds, fish, and reptiles. Reproductive failure has been reported in mammals, including seals and whales, that feed on contaminated fish and aquatic animals in polluted waterways. Many of the reproductive abnormalities observed in wildlife species have been associated with exposure to man-made chemicals, including organochlorine chemicals and pesticides, industrial waste products, and by-products of detergent surfactants, some of which have been shown to be weak estrogens. Many of the pesticides and chemicals associated with reproductive problems in animals and humans were banned from use in the United States during the 1970s and 1980s. However, there is still concern about exposures from chemicals that persist in the environment due to long half-lives and have the ability to bioaccumulate in fatty tissue and reach offspring transplacentally or through mother's milk.

Retrospective studies have reported a 50% decline in sperm counts in Western males and increased incidences of undescended testes, hypospadias, and an increased incidence of testicular cancer in certain Scandinavian countries. Increased incidences of fertility problems and breast cancer have also been reported. Although there is no known etiology to explain these health problems, it has been widely speculated that exposure to estrogenic chemicals in the environment may be responsible. There have been few attempts to estimate the level of environmental exposures to different estrogenic compounds, and no studies have examined the effect of administer-



Suzanne M. Snedeker

ing mixtures of estrogenic chemicals on reproductive endpoints in mammals. Some of the chemicals identified as estrogenic may also have adverse effects on reproduction not due to their estrogenicity. However, increased incidence of a rare vaginal cancer in daughters of women who took the synthetic estrogen diethylstilbestrol (DES) during pregnancy, together with reports of an increased incidence of fertility problems in some DES

daughters and increased incidence of male reproductive malformations in DES sons, suggest that reproductive tissues can be affected by *in utero* exposure to estrogens. It has not been substantiated that chronic, low-dose environmental exposures to estrogenic chemicals, *in utero* and through the reproductive years, cause reproductive abnormalities similar to those related to DES. Chemicals that are not estrogenic are also known to have adverse effects on reproduction by affecting endocrine pathways, which may influence the metabolism of female or male sex steroids.

To address these questions, Suzanne Snedeker and her colleagues in the Environmental Toxicology Program at the NIEHS are designing studies using the rat to determine if low-dose, chronic exposures to selected estrogenic chemicals and other chemicals known to disrupt endocrine pathways affect reproductive systems of mammals. These studies are anticipated to begin in 1994.

Levels of exposures will include low doses that are similar to levels of the chemicals found in the environment, as well as higher doses associated with occupational exposures. Chemicals will be administered singly as well as in mixtures to mimic environmental exposures. Exposures and assessments of reproduction will be carried out over multiple generations, and recovery from any observed effects will be assessed

in succeeding, nonexposed generations. Because the incidence of certain cancers has been shown to be affected by *in utero* exposure to estrogens, and standard carcinogenicity bioassays do not cover *in utero* exposures, selected reproductive tract and endocrine tissues will be examined for preneoplastic and/or neoplastic changes. Reproductive changes will be assessed through measures of fertility, spermatogenesis in males and cyclicity in females, pup viability, and changes in serum testosterone, estrogen, progesterone, luteinizing hormone, and follicle-stimulating hormone. Tissue will be examined for changes, including histopathological changes, that indicate estrogenization of females, or feminization in males. For example, in males exposed to estrone *in utero*, the normal cuboidal epithelium in the coagulating gland and seminal vesicle becomes "feminized," forming a stratified squamous epithelium, similar to that found in the female vagina during estrus. In females, estrogens can cause the vagina to open early, and female rodents exposed to DES *in utero* have an increased incidence of abnormal coiling of the oviduct.

Because only a limited number of chemicals can be included in this study, selection of chemicals will be based on 1) evidence for estrogenicity or disruption of reproductive endocrine pathways, 2) evidence for transfer to offspring transplacentally or via breast milk, 3) current widespread use or persistence of the chemical or metabolites in the environment, 4) ability to enter the food chain via groundwater, sewage contaminants, as residues on food, or by accumulation in seafood, 5) evidence of occupational exposure in industrial or agricultural applications, and 6) potential for affecting reproductive or endocrine endpoints. These studies should provide a basis for determining if exposures to low levels of chemicals, which affect endocrine pathways, cause reproductive disorders in mammals including humans.

Goldman Elected Chair of NTP Executive Committee

Lynn Goldman, assistant administrator for the EPA's Office of Prevention, Pesticides, and Toxic Substances, has been elected chair of the Executive Committee of



Lynn R. Goldman

the National Toxicology Program. The NTP coordinates toxicology research within the agencies of the Department of Health and Human Services, which include laboratories and staff within the NIEHS, the National Cancer Institute (both within the National Institutes of Health); the Centers for Disease Control's National Institute of Occupational Safety and Health; and the FDA's National Center for Toxicological Research.

Before joining EPA in 1993, Goldman served in the California Department of Health Services as a state environmental epidemiologist. She received an NIEHS National Science Research Award in 1984-85.

Olden Meets with National Tribal Environmental Council

Kenneth Olden, NIEHS director, and members of the Executive Committee of the NIEHS traveled to Jemez Pueblo in Central New Mexico to see and discuss environmental health problems of Native Americans. Of particular interest and concern was the unusually high incidence of childhood asthma.

The visit was arranged by attorney Samuel Winder, the executive director of the National Tribal Environmental Health Council, based in Albuquerque, New Mexico. The council is made up of representatives of more than 30 Native American governments throughout the United States. The NIEHS will continue to pursue environmental issues with the members of the council at its annual meeting in Nevada in December.

"Childhood asthma is a growing concern nationally, as is asthma among all age groups," Olden said. "Research partnerships with tribal governments may hold the answer to the question of how environmental exposures fuel this worrisome trend."

Olden has been active in outreach to community groups with environmental health concerns throughout the United States. In February, the NIEHS was the lead agency in coordinating a major national meeting in Alexandria, Virginia, on environmental justice, the concern that minorities and lower socioeconomic groups are exposed to environmental hazards in disproportion to their numbers because of where they live and work. The meeting brought together scores of community-group leaders and scientists and regulators from within the federal government. Winder chaired one of the sessions at this conference.

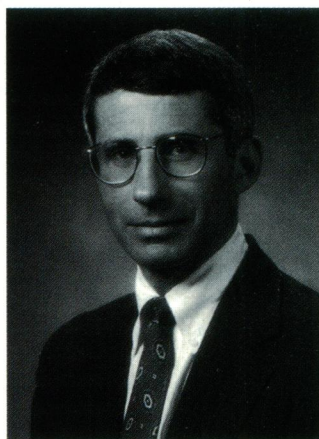
Fauci Visits NIEHS

Increased collaboration between two NIH institutes was a central theme as Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) visited the NIEHS.

Fauci, a member of the National Academy of Sciences and one of the most visible institute directors at the National Institutes of Health, is an internationally known researcher on the pathogenesis and treatment of immune-mediated diseases, most notably AIDS. At the NIEHS, Fauci gave a presentation outlining the overall mission and organizational structure of the NIAID, highlighting areas of current and potential future collaboration between the NIAID and the NIEHS. He noted that the institutes have several productive interactions, specifically in the areas of AIDS and asthma, and that these interactions should be broadened.

Fauci was the latest of six NIH institute directors to present a seminar and discuss programs of mutual interest with NIEHS scientists and other senior staff. Director Kenneth Olden initiated the visitation and seminar program shortly after he became director in June 1991, in order to foster closer working relationships between the NIEHS and its sister institutes.

"Environmental health sciences is a very broad mandate," Olden said. "It is essential that there is strong interaction between our institute and all other institutes, to obtain the most benefits medically and scientifically from the science being done throughout the National Institutes of Health."



Anthony S. Fauci

The Seventh Annual Report lists 180 chemicals, including 173 from the earlier 6 annual reports and 7 additional substances or groups of substances, including radon (listed as known to be a carcinogen) and ceramic fibers, glass wool, glycidol, hexachloroethane, tetra-nitromethane, and 4-vinylcyclohexene diepoxide (all listed as reasonably anticipated to be a carcinogen). Listing of a substance in the Annual

Report on Carcinogens is mandated by Public Law 95-622 and is for informational purposes only. Scientists from the National Toxicology Program and other federal health research and regulatory agencies evaluate the substances listed in the annual report. The listing of a substance in the annual report is descriptive and qualitative and represents an initial step in hazard identification, which is generally considered the first step in risk assessment. A risk assessment must be conducted to estimate the potential for a substance to harm human health. The National Toxicology Program does not conduct risk assessments for substances in the annual report. Such risk assessments are the purview of the appropriate federal, state, and local health regulatory and research agencies.

Seventh Annual Report on Carcinogens

The Seventh Annual Report on Carcinogens was submitted to Congress by Health and Human Services Secretary Donna Shalala on 24 June 1994. The report was prepared pursuant to Section 301(b)(4) of the Public Health Service Act, which requires that the Secretary of HHS publish an annual report which contains a list of all substances that are known to be carcinogens or may reasonably be anticipated to be carcinogens and to which a significant number of persons residing in the United States are exposed. The report also contains other information about carcinogenic substances.